DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

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Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

By Certified Mail – Return Receipt Requested
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NOV 17 2004

Warning Letter

Daniel Amsterdam, Ph.D.
Erie County Medical Center Corporation
462 Grider Street
Buffalo, New York 14215

Dear Dr. Amsterdam:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from July 12 through July 21, 2004. FDA investigator Kim Downing met with you to review your conduct of a clinical study entitled [redacted] FDA conducted this inspection under the agency's Bioresearch Monitoring Program that includes inspections designed to review the conduct of research involving investigational devices.

At the end of the inspection, a Form FDA 483, Inspectional Observations, was issued and discussed with you. We received and reviewed your written response to the Form FDA 483, dated August 4, 2004, addressed to FDA New York District Director, Mr. Jerome Woyshner.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational devices, as published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 812 (available at http://www.access.gpo.gov/nara/cfr/index.html). The applicable provisions of the CFR are cited for each violation listed below.

1. **You failed to protect the rights, safety, and welfare of the subjects under your care, and you failed to ensure that the investigation was conducted according to the investigational plan, the signed agreement, and applicable FDA regulations, including Part 50.**
[21 CFR § 812.100].

   A. Protocol sections 8.0 and 9.0 require that enrolled subjects be between the ages of 18 and 55 and able to sustain venipuncture. Subjects with life

threatening illnesses (with the exception of [redacted] as well as those with suppressed immune systems, were to be excluded from the study. You enrolled 225 low risk subjects in the study, but you failed to document that the subjects met the enrollment criteria of health status and age. Employment or other records located during the inspection provided the date of birth for only 15 of the 225 low risk subjects. One of the 15 retrieved records showed that you enrolled subject [redacted] in the study although this subject was too old to participate in the study.

In your letter, you state that you "assumedly took for granted the observation of the low risk patients as being within the inclusion age criteria as this was known from employment records."

B. You violated the protocol and the requirements for obtaining informed consent by conducting repeat testing of 11 subjects. The protocol and informed consent form [redacted] do not provide any circumstances by which subjects could be recalled to the clinic for additional testing. The protocol required the drawing of a second finger stick blood sample during the study visit to conduct a duplicate test only in the case when the finger stick and venous whole blood [redacted] results were discordant. Nevertheless, you requested that 11 subjects return to the clinic on a later date to have a blood sample collected a second time by venipuncture and finger stick. For eight subjects in the table below, the finger stick and venous whole blood results were **not** discordant, but you obtained a second finger stick blood test. Furthermore, three subjects had discordant results, but a second finger stick sample was not collected at the initial visit for duplicate testing, as the protocol required.

VISIT 1						VISIT 2			VISIT 3		
Subject	Date	FS	FSR	WBR	Discordant	Subject	Date	FS	Subject	Date	FS
[redacted]	11/08/02		R	R	NO	[redacted]	4/04/03				
	11/04/02	1	R	R	NO		11/20/02	1	[redacted]	11/27/02	2
	11/19/02		R	R	NO		12/03/02				
	11/20/02		R	R	NO		04/02/03				
	12/20/02		NR	NR	NO		4/03/03				
	2/13/03		NR	R	YES		2/21/03				
	2/13/03		R	R	NO		2/20/03				
	2/13/03		R	R	NO		2/20/03				
	2/13/03		NR	R	YES		2/20/03				
	2/27/03	1	NR	R	YES		3/30/03	2			
	3/10/03	2	NR	NR	NO		4/04/03	1			

FS = Number of Finger Sticks
FSR = Finger Stick Result
WBR = Whole Blood Result
R = Reactive
NR = Non-Reactive

In your letter, you explain "there was discrepancy between the laboratory and the clinic site [redacted] test results prompting a participant call back to resolve this problem" and that the "protocol did not preclude call-back." We disagree, for the reasons stated above.

Furthermore, in your letter you agree that additional finger sticks were performed on three participants, and explained that you repeatedly tested subject [redacted] because you obtained two negative results from a known [redacted] subject. In your response you do not explain why a second finger stick is obtained on the eight subjects when the finger stick and venous whole blood [redacted] results are not discordant. You also agree that there was failure to obtain a second finger stick sample on three occasions when it was necessary.

C. You violated the protocol by having two separate groups conduct subject and control testing for this study, and each group failed to run daily controls. The [redacted] Clinic ("Clinic") tested finger stick and whole blood samples, and Laboratory Medicine ("Lab") tested plasma and serum samples. The protocol, section 15.0 requires that controls be run daily at a minimum. Controls were not run on the following testing days for 46 subjects.

Date	Site	[redacted] Lot#	Subject(s)
11/15/02	Lab	[redacted]	[redacted]
12/4/02	Lab		
2/21/03	Lab		
11/22/02	Clinic		
11/26/02	Clinic		
2/21/03	Clinic		
2/24/03	Clinic		
3/14/03	Clinic		
4/4/03	Clinic		

The Form FDA 483 noted only those violations at the Lab dated 2/21/03 and violations at the Clinic dated 2/24/03 involving eight subjects. Your response acknowledges "control testing was required" and you attribute your omission of control testing to clerical errors, specifically the incorrect recording of date and lot number. Please explain the violations on the additional dates listed above and provide evidence of corrective action.

D. You violated protocol section 10.0 which provides that "Samples will be sent to the [redacted] daily." Review of the specimen shipping forms shows that you failed to ship the samples to the central laboratory each day for 98 of 102 records reviewed during the inspection.

Specimen #(s)	Date collected	Date Shipped
[redacted]	11/27/02	11/29/02
	4/2/03	4/4/03
	11/26/02	11/29/02
	11/27/02	11/29/02
	4/3/03	4/4/03
	2/13/03	2/14/03
	2/13/03	2/14/03
	2/13/03	2/14/03
	2/20/03	2/25/03
	2/21/03	2/25/03
	2/26/03	2/27/03
	2/24/03	2/25/03
	2/24/03	2/27/03
	2/25/03	2/27/03
	2/26/03	2/27/03
	3/6/03	3/10/03
	3/7/03	3/10/03
	2/21/03	2/25/03

The investigator included only 33 of the 98 violations listed above on Form FDA 483. In your letter you agreed that the examples noted on Form FDA 483 were correct.

E. You and your staff failed to complete the "Proficiency Panel Testing" prior to initiation of subject study testing. You enrolled and tested subjects beginning October 17, 2002, but the testing personnel did not perform the "Proficiency Panel Testing" until the period of October 21 through October 30, 2002.

Furthermore, three of nine individuals performing the proficiency testing reported the incorrect test result for Sample 4. No comments or documentation of corrective action or retraining are noted on the form. In addition, the extent of testing by untrained operators is not known because the subject testing results forms do not include operator's initials.

This violation was not included on the Form FDA 483.

F. You violated protocol section 7.3 which provides that the clinical investigator will "assure that all study results are reported to the study participants and those participants receive appropriate follow-up counseling. Once confirmation testing is available, the [clinical investigator] will notify the participant of the results and be responsible for assuring that all required follow-up counseling is provided." The counseling was required to be documented on the [redacted] *Clinical Trial Participant Counseling Form.* You failed to assure that subjects notified of reactive [redacted] tests were recalled for notification of confirmation testing and provided with follow-up counseling. As shown in the table below, for seven of fourteen low risk subjects' records reviewed during the inspection, no follow-up counseling documentation was found in case history records or on the [redacted] *Clinical Trial Participant Counseling Form.*

Subject	Test Date	[redacted] Results Finger stick/Whole Blood/Plasma/Serum			
[redacted]	11/04/02	R	R	NR	NR
	11/20/02	R	R	NR	NR
	11/27/02	NR	R	NR	NR
	11/19/02	R	R	NR	NR
	11/20/02	R	R	NR	NR
	2/13/03	NR	R	R	NR
	2/13/03	R	R	NR	NR
	2/13/03	R	R	R	NR
	2/13/03	NR	R	NR	R

You explain that you recruited [redacted] as Co-Investigator to oversee the clinical portion of this study, including subject counseling. You explain on your 483 response letter that, "none of the four [redacted] results were a matched set of reactions. Therefore, the patients were not counseled as positive patients but as discrepancies with the [redacted] test device." This response does not explain why there are no counseling records, and how you plan to correct this deficiency.

2. **You failed to maintain accurate and complete records of each subject's case history, including data on the condition of each subject upon entering, and during the course of, the investigation. [21 CFR § 812.140(a)(3)].**

A. As described in item 1.A above, you failed to document that the 225 enrolled low risk subjects met the enrollment criteria of health status and age.

B. The initial informed consent form signed by subject [redacted] was not available for review during the inspection.

In your letter you state the consent form for subject [redacted] "could not be readily recovered" and that you will attempt to secure a statement from the subject attesting that consent was originally obtained. Please provide an update on securing consent.

This letter is not intended to contain an all-inclusive list of deficiencies in your clinical study of investigational devices. It is your responsibility as the clinical investigator to ensure adherence to each requirement of the law and applicable regulations and to protect the rights, safety, and welfare of subjects under your care.

You should notify this office, in writing, within fifteen (15) business days of receipt of this letter, of the steps you plan to implement to prevent the recurrence of similar violations in future studies. Your response should include any documentation necessary to show that correction has been achieved.

This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspection. Please be advised that failure to implement effective corrective actions and/or the commission of further violations may result in the initiation of enforcement action(s) without further notice. These actions could include injunction and initiation of clinical investigator disqualification proceedings, which may render you ineligible to receive investigational devices.

Please send your written response to:

Janet K. White
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, Maryland, 20852-1448
Telephone: (301) 827-6221

We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,

James S. Cohen, J.D.
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research